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Integrating Imaging into Clinical Practice in Inflammatory Bowel Disease

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Key Words
Inflammatory bowel disease · Monitoring · Mucosal healing · Therapy success · Magnetic resonance imaging · Colonoscopy · Calprotectin

Abstract
Imaging is an important component for the monitoring of therapeutic success and disease control in patients with IBD. Colonoscopy is still the gold standard for imaging of disease activity. It is questionable, however, whether 'standard' or 'routine' imaging procedures max contribute to improved IBD therapy. There are good arguments for a problem driven imaging approach in IBD. Subsequently, the schedule of monitoring examinations should depend on the disease course (mild vs. severe) and the treatment used. Bowel ultrasound where available may substitute for endoscopy in many circumstances. New endoscopic techniques will be available at specialized centers for specific management questions. Applying these individualized strategies, imaging/monitoring will pay off for better disease control and better quality of life for IBD patients in the future.

Introduction

Integrating imaging into clinical practice is an important challenge for physicians treating inflammatory bowel disease (IBD) patients. This is a special case as there has been a change in the view of how clinical practice in IBD management should ideally be. Whereas the clinical disease presentation and clinical symptom control had been the main focus in IBD treatment in the past years and the treatment was aimed at achieving a symptom free situation for the patient, new treatment goals and paradigms have entered treatment algorithms in IBD. Mucosal or even histological healing, 'sustained deep remission', 'treat to target' and 'target to achieve' are new terms that have been introduced in discussions regarding the management of IBD patients (partially without sufficient evidence from clinical trials). These new treatment goals have changed the focus about the optimal monitoring of disease activity and, therefore, subsequently have also changed the recommendations for imaging during the course of IBD. At present, we face important discussions about when and how often to apply imaging techniques in IBD patients. This is further complicated by the fact that several imaging techniques are available only in certain countries. In North America and Great Britain, CT

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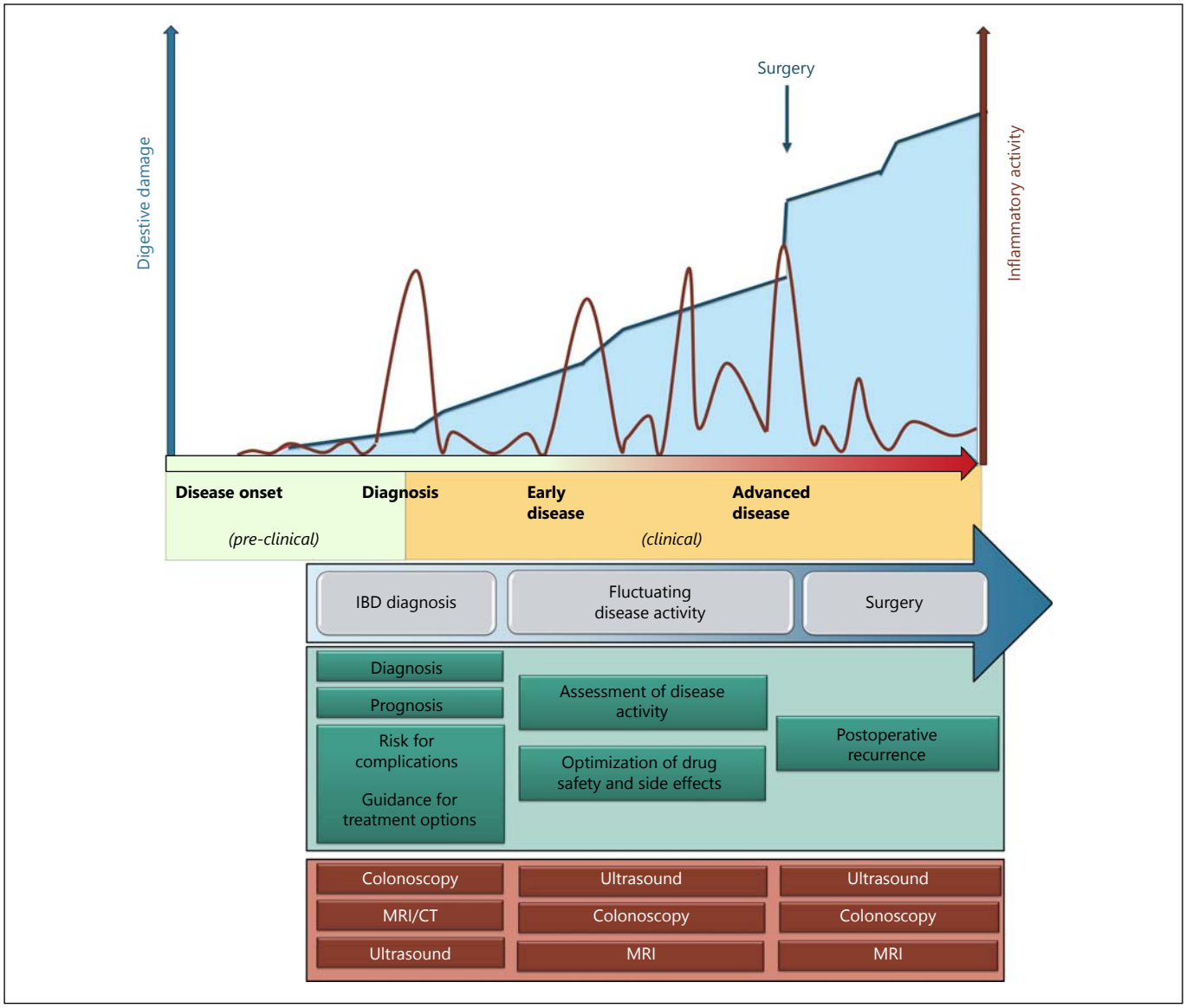

Fig. 1. Development of CD over time. Different clinical situations (gray) require diagnostic procedures and disease monitoring. The purpose of why such procedures will be necessary or undertaken is coded in green. The different diagnostic procedures performed to answer the clinical questions are in the red fields.

scans are much easily available as compared to MRI. In contrast, in Central Europe, MRI is preferred as compared to CT scans and further developed with new evaluation software. In addition, in several European countries, ultrasonography (US) has become a standard technique for monitoring the IBD patients whereas in other countries such as the United States, it is only in the hand of radiologists making it difficult to be applied for monitoring the IBD patients. In the following article, the future of imaging and monitoring in IBD is discussed from a viewpoint rather derived by personal clinical experience than robust and prospective clinical evidence, that is, on a comparable ground work as most of the current literature on mucosal healing and treat to target.

When Do We Need Imaging Tools for IBD Patients?

Usually, the first time imaging is used – or at last should be used – in a suspected case of IBD is when the occurring symptoms can be associated with the disease (fig. 1). Imaging is used for confirming the diagnosis and

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for differential diagnosis [1]. Still, we do not have a gold standard for diagnostic procedures in Crohn's disease (CD) and ulcerative colitis (UC). Most guidelines, however, for example the ECCO guidelines [1], clearly state that endoscopy should be the basis of diagnosis (fig. 1). In CD, further imaging techniques, such as US and MRI or CT scans, are highly valuable for evaluating the small bowel [1]. Indeed, performing a small bowel evaluation with one of the aforementioned diagnostic tools is explicitly recommended in every initial diagnostic procedure to establish the diagnosis of CD, irrespective of the findings by ileocolonoscopy, according to the ECCO guidelines [2]. Imaging techniques can also help in the evaluation of the prognosis, the risk for complications and provide guidance regarding the initial treatment options [3–7] (fig. 1). Whereas this is not very much disputed, the indication and schedule for further imaging during fluctuating disease activity is much more prone to controversies. If clinical symptoms are not sufficient to evaluate the success of therapy, and at the time when a status of being free of clinical symptoms is not accepted anymore as the treatment goal of IBD therapy, other parameters obviously must play a more important role. Mucosal healing of course can only be evaluated by taking a look at the mucosa and in fact only by taking mucosal biopsies [8, 9]. It is disputable whether deep remission can also be evaluated by other imaging technics such as US and MRI or CT scan [9]. In this respect, an interesting and elegant investigation (yet only published in abstract form) comparing 2 evaluation strategies in CD providing, at first, the results of endoscopy and, subsequently, findings of MRI to 4 clinical expert investigators for the procedure the other way round, revealed that the results of MRI harbored a higher impact on subsequent clinical decision making than those of colonoscopy, thus directly challenging colonoscopy's current pole position in the diagnostic algorithm of CD [10]. Eventually, assuming one would assign an even higher importance to histological healing as compared to mucosal healing derived by pure vision, the role of assessment by both endoscopy and imaging to adjust treatment or predict relapse risk may be challenged by comparative investigations with fecal calprotectin, suggesting that the correlation of the latter to histological healing may even surpass endoscopy. If we define a necessity to assess disease activity with such techniques, another point of discussion is about how often we should monitor disease activity. This subsequently leads to a point of concern about the frequency of evaluation of treatment success.

Concepts That Propose a Frequent Evaluation of Therapy Success

In recent years, several concepts have pointed to an increased requirement of evaluation of disease activity by imaging. Among those are the concepts of mucosal healing, 'sustained deep remission', 'treat to target' and 'target to achieve'. In a recent publication by the International Organization for the Study of Inflammatory Bowel Diseases, the authors state the following: 'Collectively, these data suggest that an ideal treat-to-target strategy should follow the patient every 36 months for assessment of MH (disappearance of ulcers) with colonoscopy (or MRE or US in patients who cannot be adequately assessed with colonoscopy). … Six-month intervals between colonoscopy procedures may be a reasonable compromise between selecting a time after which additional MH is unlikely to occur and a time interval between procedures that would be acceptable to patients' [11]. This obviously means that after a change in therapy, at least every 6 months, a colonoscopy should be performed to evaluate whether this change in therapy has been successful. One of the reasons to suggest this is that it appears to be acceptable for the patients. Potential acceptance by the patients may not be a perfectly robust argument to define the intervals for a diagnostic imaging procedure. Either it is necessary or it is not. If it is necessary, but not accepted by the patients, we have to find an alternative method. Also, the time between the change of therapy and the evaluation by endoscopy seems to be somewhat arbitrary, for instance, different treatments obviously have different response times. An anti-integrin or anti-metabolite therapy will take more time for response as compared to a therapy using antibodies to tumor necrosis factor. Subsequently, it appears to be obvious that the selection of the imaging modality and the interval between the treatment change and the imaging procedure should be dependent on the therapy that is chosen.

Furthermore, it is doubtful whether patients would accept an imaging/disease monitoring strategy as outlined in figure 2. In contrast, it rather appears that this simply would and will not be practicable.

In contrast, in a recent manuscript by Bouguen et al. [12], the authors conclude that 'repeated assessment of endoscopic disease activity with adjustment of medical therapy to the target of mucosal healing is feasible in clinical practice in patients with UC, and seems to be of benefit'. Of course, endoscopic assessment is much easier in patients with UC as usually no complete colonoscopy is necessary. The question, however, is whether repetitive

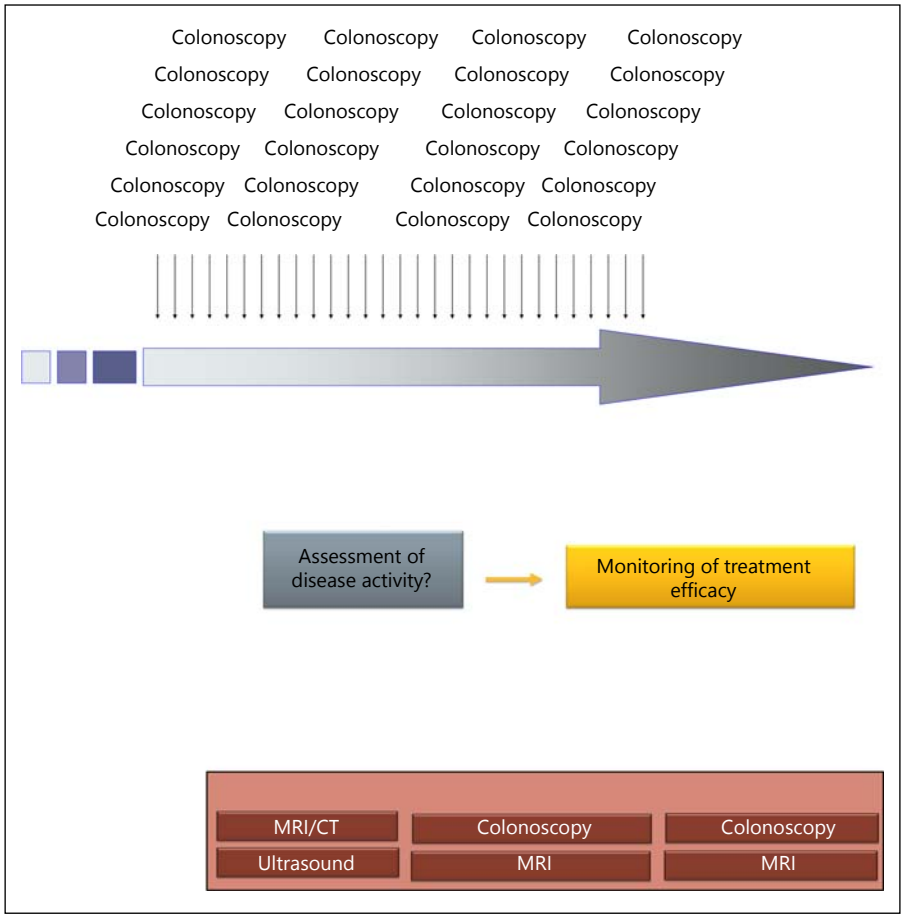

Fig. 2. Imaging and monitoring as suggested mainly by endoscopy-focused gastroenterologists. Patients may not accept such a strategy.

calprotectin measurements could replace endoscopies as it is well known and evident from published literature that calprotectin correlates to histology even better than endoscopic evaluation in patients with UC [13–15]. In the 60 patients included in this retrospective analysis mentioned above, 159 endoscopic procedures were performed including 92 ileocolonoscopies and 67 flexible sigmoidoscopies [12]. Less than 50% of the patients included had 3 consecutive endoscopic procedures, and only 8 had 4 consecutive endoscopic procedures [12]. It is doubtful whether from those selected patient with a majority of only 2 endoscopic procedures, it can be concluded that repeated endoscopic control of mucosal healing or therapy success is really feasible [12].

Another publication from the same authors concluded that regular endoscopic assessment of mucosal healing and endoscopic disease activity and subsequent adjustments of medical therapy increased the likelihood of mucosal healing [11]. Again, this was a retrospective study with some risk of selection bias. After a median follow-up period of 62 weeks in the included 67 patients (out of 161 that had at least 2 endoscopies), a total of 161 endoscopic procedures were performed, including 151 ileocolonoscopies or flexible sigmoidoscopies. Only 31% underwent 3 consecutive endoscopic procedures, and only 6 patients (9%) underwent 4 consecutive endoscopic procedures [11]. Similar to UC patients, it appears to be doubtful whether it can be concluded that repetitive endoscopy is feasible, from these data, in the long-term treatment of CD patients (fig. 2). Furthermore, endoscopy has not been compared to other strategies of monitoring of therapy success such as calprotectin or US [4, 16, 17].

US Allows Frequent Evaluation of Therapy Success

US techniques have long been used for the monitoring of therapy success in patients with UC and CD. US has a number of advantages such as transmural evaluation of the bowel wall (in contrast to endoscopy and similar to CT/MRI), rapid information without delay or preparation (in contrast to endoscopy, MRI or CT scan, e.g. with

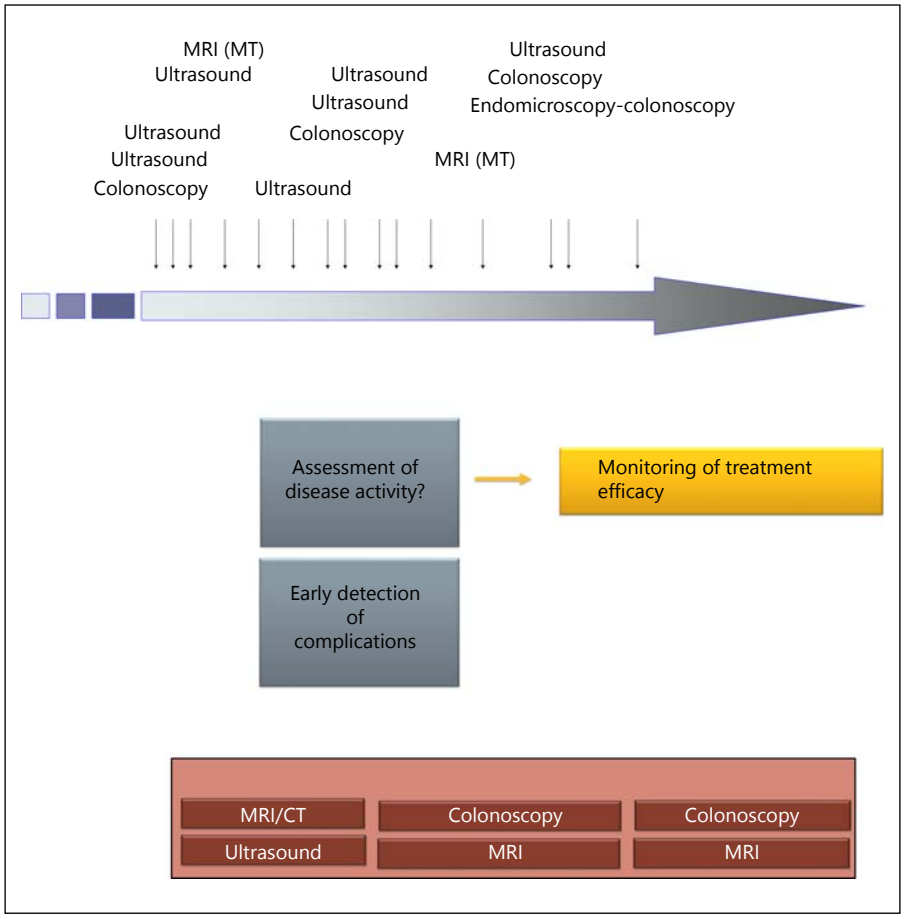

Fig. 3. Individualized, patient- and situation-adapted strategy for imaging and disease monitoring as suggested in this manuscript.

Table 1. Imaging modalities in IBD

	Endoscopy	US	CT	MRI
Mucosa	+++	++	++	++
Transmural	–	+++	+++	+++
Fistula	+	++	+++	++++
Abscess	–	++	+++	+++
Strictures	++	+++	+++	+++
Operator department	+	++	+	+
Standardized images	+	+	++++	++++
Irradiation	no	no	yes	no

the question: 'does a change of symptoms reflect a flare?'), no X-ray exposure (in contrast to CT scans, similar to MRI), evaluation of motility (live on-site in contrast to endoscopy, CT scan and MRI, which is important to evaluate functional impairment), the possibility of evaluating patient history and symptoms in parallel (e.g. 'where/there is the maximum of pain?') (table 1). In contrast to the frequent notion that US is a very subjective method, there are objective parameters in bowel US, and an assessment of these should be requested (table 1). Bowel wall thickness at least in certain segments can be objectively quantified and reliably monitored. Therefore, it can be used as a parameter of therapy success. The relevance of measuring bowel wall thickness has been demonstrated by a number of studies, and sensitivities of 75–94% and specificities of 67–100% have been reported [1]. As out-

lined in the ECCO consensus on imaging, a recent meta-analysis of 7 prospective, well-designed diagnostic trials indicated that a threshold of >3 mm bowel wall thickness as cut-off value possesses a sensitivity and specificity 88 and 93%, respectively, for acute inflammation in CD, while a cut-off level of >4 mm is associated with a sensitivity and specificity of 75 and 97%, respectively [18].

Subsequently, the ECCO guidelines on imaging state that 'US, CT and MRI have a high and comparable diagnostic accuracy at the initial presentation of terminal ileal CD' (statement 3A) [1]. They further explain that 'US, CT, MRI and white blood cell scintigraphy can be used to assess disease activity in CD of the terminal ileum' (statement 3B) [1]. Also, for monitoring purposes, US is regarded to be useful as outlined in statement 4B: 'transabdominal US and MRI have a high accuracy for assessing the activity and severity of Crohn's colitis (EL:1b, RG:A); the performance in UC is less clear and the role of CT for distinguishing quiescent from active colonic IBD is currently not defined' [1]. Subsequently, US in combination with calprotectin values (which will not be discussed here as this is out of the focus of this article) may perfectly complement and indeed at least frequently well replace endoscopy in the suggested tight monitoring of therapy success and respective adjustments in IBD patients (fig. 3).

Summary

Imaging for the monitoring of therapeutic success and disease control (or 'mucosal healing') will be an essential component of future IBD patient care. However, imaging should be problem driven ('is there a question to answer?'; 'will the results of imaging change treatment?'), and not strict and rigid as it is on regular basis as suggested by some recent publications. Furthermore, the schedule of monitoring examinations should depend on the disease course (mild vs. severe) and the treatment used (e.g. antibodies to tumor necrosis factor therapies versus anti-integrin antibodies). US may substitute for endoscopy in many instances for the monitoring of IBD patients (fig. 3). New endoscopic techniques may be available at specialized centers for specific management questions; however, they will not reach a general distribution in the foreseeable future. Applying these strategies, imaging/monitoring will pay off for better disease control and better quality of life for IBD patients in the future.

Disclosure Statement

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